An Interview with Dr Camidge, professor of medicine-medical oncology and the director of the Thoracic Oncology Clinical and Clinical Research Programs at the University of Colorado Cancer Centre – Anschutz Medical Campus in Aurora. (February 2025).

Lorlatinib (Lorbrena) has become the frontline standard of care for patients with *ALK*-positive non–small cell lung cancer (NSCLC) after extended follow-up data emphasized the importance of exposing patients to the potential benefits of this agent early in the treatment sequence rather than after the use of other ALK inhibitors, according to D. Ross Camidge, MD, PhD. He also advocated for a measured, patient-centered approach to anticipating and mitigating lorlatinib-related toxicities.

The phase 3 CROWN trial (NCT03052608) compared lorlatinib vs crizotinib (Xalkori) in patients with systemic therapy–naive, advanced, *ALK*-positive NSCLC.[1] Findings presented at the 2024 ASCO Annual Meeting showed that at a median follow-up of 60.2 months for patients who received lorlatinib (n = 149) and 55.1 months for those who received crizotinib (n = 147), the median progression-free survival (PFS) was not yet reached (NR; 95% CI, 64.3 months-NR) vs 9.1 months (95% CI, 7.4-10.9), respectively (HR, 0.19; 95% CI, 0.13-0.27).

“As of June 2024, if you put cancer efficacy at the center of the decision-making equation, you would always choose lorlatinib [for this population in the frontline setting],” Camidge said in an interview with *OncLive*®.

Furthermore, the phase 1/2 B7461001 trial (NCT01970865) demonstrated the efficacy of lorlatinib in patients with *ALK*-positive metastatic NSCLC who had previously received treatment with at least 1 ALK inhibitor.[2] Exploratory subgroup analyses of this trial showed objective response rates of 39% (95% CI, 30%-48%), 31% (95% CI, 9%-61%), and 46% (95% CI, 19%-75%) with lorlatinib in patients who had previously received crizotinib and at least 1 other ALK inhibitor (n = 119), alectinib (Alecensa; n = 13), or ceritinib (Zykadia; n = 13), respectively.

In the interview, Camidge discussed ways that *ALK*-positive NSCLC management has changed in light of the 5-year follow-up data from CROWN; a lorlatinib dosing schedule that may increase the agent’s tolerability in some patients; and how biomarker test results should prompt further questions about individualized disease management.

What have been some of the most important recent updates to the *ALK*-positive NSCLC treatment paradigm?

Camidge: At the 2024 ASCO Annual Meeting, the 5-year follow-up of the CROWN study was shown. CROWN investigated lorlatinib vs crizotinib in [patients with] first-line, *ALK*-positive advanced disease. Data [from CROWN] had been out for several years, but the importance of the 5-year data was [that they] showed that the duration of benefit with starting with lorlatinib [far exceeded that obtained] with [starting with] a different ALK inhibitor and then [switching to] lorlatinib in the second line.

However, it took 5 years for [those data to mature] because we had to see that the [PFS] curve stayed up, and it did. After 5 years, the median PFS had still not been reached [in patients who started with lorlatinib].

How have the CROWN data influenced cancer treatment guidelines?

The National Comprehensive Cancer Network [NCCN] is always a little wishy-washy. It likes to give many different choices. When you look at [resources] like Elsevier Clinical Pathways, which tries to narrow the choice down. [The addition of lorlatinib to the NCCN Guidelines] raises 2 major issues. One issue is: What happens if a patient's oncologist saw them the week before [the 2024 ASCO Annual Meeting] and prescribed alectinib or brigatinib [Alunbrig]? What [does that oncologist] do? The other issue is: What's the tolerability of lorlatinib? Why was there resistance [to incorporating this agent into clinical practice]? Why did it take 5 years of data before oncologists were changing [their practice patterns]?

If your patient was already receiving alectinib, brigatinib, or any agent other than lorlatinib in the first-line setting, and then the [5-year] CROWN data came out, do you switch [to lorlatinib]? It depends. Some patients have been receiving a drug for so long, they have declared that they are tolerating the drug and that it is controlling the cancer well, and in many ways, it is the drug for their cancer. On the PFS curves [with other ALK inhibitors], a plateau of nonprogression takes approximately 2 or 2.5 years to manifest. If a patient is on the other side of that, [such as] if they have been receiving alectinib for 4 years, [they might not need to] change.

However, if [patients are at an earlier point in their treatment], some will change. The week before ASCO, I started [a patient on] alectinib, then phoned them up the following week and told them there were new data and [I was] going to switch [their therapy]. That decision to switch is a continuum [starting] the week before the ASCO data were released. It's a discussion that comes down to not whether lorlatinib is a better ALK inhibitor than alectinib or brigatinib, but whether the AEs [associated with lorlatinib] are worth the additional potential [efficacy].

What toxicity considerations should be top of mind when administering lorlatinib?

We know from the CROWN data that lorlatinib is the 'best' available ALK inhibitor to start on. However, the reason it took 5 years for [practice] to change is because lorlatinib isn't necessarily an easy drug [to tolerate]; there are many adverse effects [AEs]. Approximately 80% of patients will have to go on to receive a cholesterol- or triglyceride-lowering drug, or both.

Additionally, many patients will put on weight. Pfizer presented misleading data suggesting there isn't a cumulative weight gain [with lorlatinib] because they bundled together multiple different grades [of this AE].[3] That is blatantly not true. Your patients will increase in weight over time.

There are many other AEs—neurological AEs, mood-related AEs, sleep-related AEs, and speech-related AEs. In clinical trials [with lorlatinib], where perhaps we didn't know to look out for [neurocognitive AEs], we were asking patients if they had insight into whether they were [feeling] a little weird. The rate of [these AEs] was approximately 20%. [However], if you learn what you should ask, and you learn to ask the caregivers in the room and not just the patients, that rate becomes approximately 60%. In my experience, these AEs tend to develop relatively early within the first few months [of treatment].

The way I [manage these AEs] is to ignore the prescribing information. The [recommended dose of lorlatinib according to the] prescribing information is 100 mg once a day. [That is too much all at once to start for] some patients. You have to slowly increase exposure. I start at 50 mg [once daily]. [Lorlatinib] comes in 25-mg pills. Approximately 2 months later, I [increase the dose] to 75 mg [daily]. Approximately 2 months after that, I'll try 100 mg [daily], and many patients settle down at 75 mg. That time scale allows those neurocognitive AEs to manifest, and the risk that anything bad will happen when you're [experimenting with] lower doses is low at the beginning, so it's a safe, slow step-up that you can do. You won't hear this from Pfizer, because the prescribing information is 100 mg [daily], and they have been reluctant to push step-up dosing.

[However, these AEs are] real. Your patients will have a lot of psychiatric and neurocognitive AEs, which, if you don't ask them about, they won't volunteer. The classic example is: When you do a study in Western countries and you ask the right questions, you can get a 60% rate [of neurocognitive AEs]. However, if you do the study in China, where, for whatever reasons, [oncologists] don't ask these questions or [patients do not] volunteer these AEs for cultural reasons, the rate is 0%.

Do you see the FDA reevaluating the approved dose of lorlatinib?

Project Optimus is an initiative that the FDA has championed to say that the dose [of a given agent] put forward for efficacy maybe [does not provide] the best balance between efficacy and toxicity. [However], I don't see the FDA doing a lot of retrospective [dose adjustments with lorlatinib]. It's an effective drug, but it's a great example of where Project Optimus would have been wonderful to have been employed at the time [of its development].

How do the 5-year CROWN data affect the use of other ALK inhibitors in the NSCLC treatment paradigm?

If a patient is already receiving a drug and doing well, [they may have] found their drug, and they don't need to change. [Those drugs] will stay [part of the paradigm]. Other [ALK inhibitors] will have a notable place in history for keeping patients alive and well because they were the best drugs at the time [before lorlatinib].

How might the intracranial activity of lorlatinib affect its uptake in the paradigm?

It was interesting that that story emerged. Early on, when the CROWN data came out, oncologists were not shifting [to using lorlatinib]. They [saw] these data vs crizotinib, but [they recognized that lorlatinib was] a toxic drug.

There was a move by the company to try to push oncologists to start lorlatinib. They talked about efficacy in patients with deposits in the brain or a higher burden of disease, etc. [However], the presence of brain metastases doesn't make a difference [in lorlatinib's efficacy]. It's still the best drug [in its class], but it has not magically become the best-tolerated drug.

Where does lorlatinib ultimately belong in the *ALK*-positive NSCLC treatment sequence?

I was one of the holdouts [regarding sequencing lorlatinib with other agents]. [I thought it might be best for patients to] start on alectinib. Lorlatinib has a license post-alectinib. [I asked:] Could you [sequence alectinib before lorlatinib] to get the same net gain but have less time on the [more] toxic drug?

However, when we saw the 5-year CROWN data, if you do the algebra in your head of alectinib [followed by] lorlatinib, it was never going to be as [effective] as starting on lorlatinib. Again, if [alectinib] is the drug a patient is currently receiving, and they are doing great, that's fine for [that patient to stay on alectinib]. However, if a patient is diagnosed today, you would use a different strategy.

What are some best practices for biomarker testing in patients with NSCLC?

ALK[-mutated lung cancer] was the subtype of lung cancer that blew open the wall of biomarker testing. There was *EGFR*[-mutated disease], but *EGFR* mutations were somehow viewed as an exception, and everything else was [part of] the same [category] for many years. When *ALK* mutations [were discovered], the idea that there was a second molecularly actionable subtype of lung cancer suddenly meant maybe there's a third, and maybe there's a fourth. It has significant historical meaning.

[ALK is] commonly part of sequencing analyses, and the only aspect to pay attention to is understanding the meaning of a negative result. [Patients might think] a negative result [means they have no] biomarkers in their cancer. [However], that depends on what [mutations the oncologist tested for and how they tested]. If they just sent off a blood biopsy—one of those circulating tumor DNA tests—and it didn't show anything, that's not a true negative. It might be a convenient test.

However, [with a negative result in that case], you would see if there is tumor tissue you can sequence. The value of that tissue increases [in patients who are] never smokers, [those with] adenocarcinoma, and, to some extent, [those who] are Asian or female, although that mostly

applies to *EGFR* mutations. However, multiple papers have shown that squamous cancer has [mutational] changes and that [these changes] can occur in smokers, just at a lower frequency.

You have to ask the question: If it was your mom or your dad [with lung cancer], would you want to rest if you hadn't done the testing? No. Testing is cheap. Testing is relatively easy. A negative blood test doesn't mean a negative tumor test, but if you've explored every [test result and the patient does not] have a biomarker, then they have [one of the other] 40% to 60% of lung cancers that exist.

Is there a potential value to longitudinal biomarker testing in NSCLC?

[Some] people are trying to 'sell' you the latest drug, and they want you to believe that cancer remains addicted to a single pathway, such that a patient will switch from ALK inhibitor to ALK inhibitor. Sometimes that's true. For example, if a patient has received sequential ALK inhibitors, usually not if they start on lorlatinib, they can build up compound *ALK* mutations. [If they receive] crizotinib, then alectinib, then lorlatinib, they build little building blocks of another mutational profile, and that's what's driving their cancer. There, fourth-generation ALK inhibitors might have a role.

However, the issue is: 40% to 60% of patients' [diseases] become less dependent on ALK and bring in a second driver pathway, so [all the mutations] on the list of usual suspects can come in in a supporting role. Nobody is selling you that combination. However, in the real world, patients who jump, for example, from alectinib to lorlatinib, will have approximately a 35% to 45% response rate. That tells you that that's the frequency of on-target *ALK* mutations. Other patients will be enriched
for *KRAS* mutations, *RET* rearrangements, *EGFR* mutations, *MET* amplifications, and all the other [alterations] that can come in as second drivers.

Changing the ALK inhibitor won't make a difference there. There, you need to use a combination regimen. Or, if there aren't effective combinations you can access, you're back to pemetrexed-based chemotherapy.